				be almost impossible to evaluate all the active and inactive components of pesticides since the "inerts" are trade secrets and not identified and change over time. This would seem to be a place where experimental studies could actually provide this information by analyzing the pesticide mixture to determine all ingredients, then test them individually or in various combinations in experimental studies. Again the complementary nature of the two disciplines works. *EFSA Response:* *See also #185.* • 2453-2455: The Panel's stance on a priori analyses seems odd in that they support the use of prospective cohort studies. One of the advantages of prospective cohorts is that it is possible to look at issues not of concern when the cohort was initiated. Is the Panel suggesting this should never be done? *EFSA Response:* *Same text as comment #197.* • 2461-2463: I second this recommendation. What it is likely to show, as the literature already suggests, is that confounding is a really rare event. It should be considered in all epidemiology studies. *EFSA Response:* *Same text as comment #197.* • 2464-2468: It is true that small studies can result in "chance" statistical excesses. It is also true that small studies can result in "chance" findings that are artificially deflated. Small studies create more noise in both directions. It is not unidirectional. *EFSA Response:* *Same text as comment #197.* • 2477-2479: I am not familiar with what occurs in toxicology, but I assume the Panel also supports that toxicology studies be encouraged to provide access to raw data to other investigators and to deposit their full results and scripts, laboratory manuals, and software packages used for analyses online. *EFSA Response:* *Agree.*

201	Université de Bordeaux	FRA	8.1 Recommendations for single epidemiological studies	• 2368-2370: Prospective studies can provide a strong inference for causality. But a prospective study of mortality from diseases that may not be listed on death certificates would not be stronger than a case-control study of such disease identified from hospital or pathologic records. There are many other situations where a prospective cohort study might not be the best choice. The Throughout this document the Panel has made many such sweeping statements about epidemiology that are not accurate. Determinations about study quality based simply on the overall study design is dangerous and often wrong. • 2367-2385: Standard for epidemiologic studies. • 2388-2391: Exposure characterization should avoid "broad exposure classifications such as "never" vs. "ever" categories" but these categories are "valuable under certain circumstances" as it was demonstrated for example for smoking. So this approach is valuable, but should be avoided? • 2397-2400: I assume that "eliciting the same mode of action or toxicologic effects" does not mean the mechanism by which the pesticide accomplishes it pesticidal action. I think there is already considerable evidence to indicate that pesticides in the same chemical class may have different unintended effects, i.e., all organophosphate pesticides would not be expected to have the same effect on some disease, even though their action on the target pest may be the same. • 2412-2415: We can all agree that direct measurements (biologic or exposure) is preferred. However, in many situations pesticide exposures are intermittent, may vary from year to year, and completely change over of time. Many chronic human diseases only develop after a long latency. So it is entirely unlikely that such a massive number of repeat measurements necessary to provide an adequate number of "direct measurements" would ever be available. What would be helpful from the Panel is what combination of exposures measurement, biologic measurements, and exposure determinants would be most helpful in characterizing exposure for risk assessment. For example which is more valuable (1) a few measurements in the present, (2) a few measurements from several years in the past, or (3) a more comprehensive exposure monitoring strategy undertaken very recently and coupled with information on jobs, work tasks, and exposure determinants over a longer time period? • 2424-2431: Improved knowledge on exposure mixtures for pesticides would be helpful. In epidemiology is would be almost impossible to evaluate all the active and inactive components of pesticides since the "inerts" are trade secrets and not identified and change over time. This would seem to be a place where experimental studies could actually provide this information by analyzing the pesticide mixture to determine all ingredients, then test them individually or in various combinations in experimental studies. Again the complementary nature of the two disciplines works. • 2453-2455: The Panel's stance on a priori analyses seems odd itnthat they support the use of prospective cohort studies. One of the advantages of prospective cohorts is that it is possible to look at issues not of concern when the cohort was initiated. Is the Panel suggesting this should never be done? • 2461-2463: I second this recommendation. What it is likely to show, as the literature already suggests, is that confounding is a really rare event. It should be considered in all epidemiology studies. • 2464-2468: It is true that small studies can result in "chance" statistical excesses. It is also true that small studies can result in "chance" findings that are artificially deflated. Small studies create more noise in both directions. It is not unidirectional. • 2477-2479: I am not familiar with what occurs in toxicology, but I assume the Panel also supports that toxicology studies be encouraged to provide access to raw data to other investigators and to deposit their full results and

				scripts, laboratory manuals, and software packages used for analyses online. *EFSA Response:* *Same text as comments #197 and 200.*
202	US EPA	USA	8.1 Recommendations for single epidemiological studies	Footnote 18. line 2 It is Annex D, not Annex B Footnote 18. line 3 It is diseased from a particular disease(s) not all diseased. In epi studies, people may have different diseases and only diseases of interest (and not, say, common cold or broken finger) are counted. *EFSA Response:* *Footnote 18 has been corrected. It now reads" Annex D" in line 2. In line 3, the text "including diseased and non-diseased individuals" has been replaced by the following wording: "including individuals with and without the disease of interest".* Line 2515 What is "excess significance bias"? Is it what commonly known as publication bias? *EFSA Response:* *The term 'excess significance bias' refers to the situation in which there are too many studies with statistically significant results in the published literature on a particular outcome. This pattern suggests strong biases in the literature, with publication bias, selective outcome reporting, selective analyses reporting, or fabricated data being possible explanations (Ioannidis and Trikalinos, 2007; PMID: 17715249).* *A footnote has been added in line 2515 to clarify this point.* Line 2517 How "Highly selected population" is defined? *EFSA Response:* *When the study population of an epidemiological study consist of highly selected groups of individuals that are unrepresentative of the general population and not necessarily representative of any populations that are susceptible to precise, generally applicable definition. This may limit the generalizability of the study results because of the underlying selection bias.* Line 2527 The text leaves impression that pooling studies is necessary for enabling dose-response, whereas individual studies can be modeled as well. *EFSA Response:* *The comment is correct, but the sentence in line 2527 claim that by pooling quantitative data of individual studies the precision of quantitative risk estimates could be improved.*

203	Ministero della Salute	ITA	8.1 Recommendations for single epidemiological studies	This chapter should reflect at the end all the comments listed above (both general and specific ones). This chapter provides excellent suggestions the design of epidemiologic studies. However, some of the bullet points are not written as recommendations, and should be rephrased. In general, epidemiological studies include a large number of exposures and outcomes (eg. Cohort studies). The recommendations do not take this into account. Issues relevant to multiple comparison testing should be considered *EFSA Response:* *Such detailed statistical methodology considerations beyond the broad statements in Table 2 might be addressed in a subsequent guidance document if one is mandated.*
204	Uniformed Services University	USA	8.1 Recommendations for single epidemiological studies	(Lines 2412-2415): Direct measurements (biologic or exposure) are often preferred, though not always. Pesticide exposures may be intermittent, could vary from year to year, and even change completely over of time. Many chronic human diseases have long latencies, thus it is quite unrealistic to expect that so many direct measurements could be taken in a large enough study population to sufficient provide statistical power. Additionally, it is important to consider that many pesticide exposures today are from compounds with short half-lives, so measurements that may be most relevant to acute outcomes may not be relevant to chronic/long latency outcomes. In some cases, exposure assessment may be more relevant via carefully designed, structured questionnaire about the timing, duration, specific use, and intensity of pesticide use. *EFSA Response:* *It is not intended that direct measurements should necessarily be the sole method of assessment of exposure. Elsewhere the document discusses how such methods can be used with other methods to construct exposure histories.* *Line 2414 has been amended as following: "... metering/biological monitoring), possibly in conjunction with other methods of exposure assessment which are more practicable or even necessary for large studies and historical exposures". New studies should explore novel ways of personal..."*
205	Dept. Food Safety, Nutrition, Veterinary Public Health- Istituto Superiore di Sanità	ITA	8.1 Recommendations for single epidemiological studies	2376-8: combined exposure to multiple chemicals may be considered a confounder from the strict standpoint of the use of epidemiological data for regulating one pesticide. On the other hand, a large part of human exposure scenarios involve the combined and concurrent exposure to several pesticides. Therefore, multiple exposures should be considered distinct from established "confounders" Suggested change: "A wide range of potential confounding variables (lifestyle, socioeconomic factors, etc.) as well as the co-exposure to other chemicals, and in particular to other pesticides, should be measured or accounted for..." *EFSA Response:* *See reply to comments #30 and 113.*
206	Dept. Food Safety, Nutrition, Veterinary Public Health- Istituto	ITA	8.1 Recommendations for	Lines 2380-81 Nutrient status should be additionally mentioned a significant effect modifier side to genetics, for instance iodine status is a relevant effect modifier for thyroid-acting pesticides (see e.g.

	Superiore di Sanità		single epidemiological studies	https://www.ncbi.nlm.nih.gov/pubmed/28073049) Suggested change "These can include genetic polymorphisms data, such as paraoxonase-1 type, and nutrient, e.g. iodine, status" . *EFSA Response:* *Thank you for this suggestion.* *This clarification has been included in line 2380 (section 8.1.a.5).*
207	ECPA	BEL	8.2 Surveillance	See comments above under section 5.3. *EFSA Response:* *See reply to comment #141.*
208	US EPA	USA	8.3 Meta-analysis of multiple epidemiological studies	Footnote 18. line 2 It is Annex D, not Annex B Footnote 18. line 3 It is diseased from a particular disease(s) not all diseased. In epi studies, people may have different diseases and only diseases of interest (and not, say, common cold or broken finger) are counted. Line 2515 What is "excess significance bias"? Is it what commonly known as publication bias? Line 2517 How "Highly selected population" is defined? Line 2527 The text leaves impression that pooling studies is necessary for enabling dose-response, whereas individual studies can be modeled as well. *EFSA Response:* *Same text as comment #202.*
209	ECPA	BEL	8.4 Integration of epidemiological evidence with other sources of information	As noted for section 7, the scientific opinion does not provide explicit recommendations for incorporating epidemiology evidence into systematic reviews. The recommendations section should include an explicit discussion of how EFSA plans to integrate evidence as part of its pesticide risk assessment and management activities. *EFSA Response:* *The text in the Recommendations is a brief summary of section 7.2, where more details are given. Anyway, a detailed methodology cannot be given at this time, only a number of principles to make the methodology work in practice.* *The following text has been added in line 2540: "A systematic integration of data from multiple lines of evidence should be based on a WoE analysis accounting for relevance, consistency and biological plausibility using modified Bradford Hill criteria. The principles underlying this framework are described in section 7.2 and summarized in Figure 5".*